

WHAT IS CLAIMED IS:

1. A method for improving an electron density map of an experimental crystal structure, comprising the steps of:

- a. forming a model electron density map of a model crystal structure;
- b. forming model histograms of model electron densities in identified

5 protein and solvent regions of the model electron density map;

- c. fitting a model probability distribution function defined by

$$p(\rho_T) = \sum_k w_k \exp \left\{ -\frac{(\rho - c_k)^2}{2\sigma_k^2} \right\}$$

10 to the model histograms, where k is separately indexed over the protein and solvent regions of the model map, $p(\rho_T)$ is the probability of an electron density at a point, w_k is a normalization factor, ρ is electron density, c_k is a mean value of ρ , and σ_k is a variance of ρ , where the fitting determines the coefficients w_k , c_k , and σ_k ;

15 d. determining a set of experimental structure factors from x-ray diffraction data for the experimental crystal and forming an experimental electron density map;

e. forming separate experimental histograms of experimental electron densities over protein and solvent regions of the model electron density map;

- f. fitting an experimental probability distribution function defined by

$$p(\rho_T) = \sum_k w_k \exp \left\{ -\frac{(\rho - \beta c_k)^2}{2(\beta^2 \sigma_k^2 + \sigma_{MAP}^2)} \right\}$$

20 to separate protein and solvent regions of the experimental histograms, where β is an expectation that an experimental value of ρ is less than a true value and σ_{map} is a variance, where the fitting determines the coefficients β and σ_{map} ;

g. determine from the probability distribution function the overall experimental log-likelihood of the electron density in the protein and solvent regions of the experimental map;

h. determine how the log-likelihood of the electron density of the protein and solvent regions of the experimental map would change as each experimental structure factor changes to output a revised log-likelihood of any value of each experimental structure factor; and

i. forming from the revised log-likelihood of experimental structure factor values a new set of structure factors and returning the new set of structure factors to step (f) to iterate the process.

2. A method according to Claim 1, wherein step a. further includes the step of selecting the model crystal structure to be similar in size, data resolution, and atomic displacement factors to the experimental crystal.

3. A method according to Claim 1, wherein step b. further includes the step of identifying protein and solvent regions by designating all points within a selected distance of an atom as "protein" and all other points at "solvent."

4. A method according to Claim 2, wherein step b. further includes the step of identifying protein and solvent regions by designating all points within a selected distance of an atom as "protein" and all other points at "solvent."

5. A method according to Claim 1, wherein step h. includes the steps of forming a Taylor's series expansion of the log-likelihood of the experimental map and evaluating terms of the Taylor's series expansion using a Fast Fourier Transform.

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6. A method for improving an electron density map of an experimental crystal structure, comprising the steps of:

a. forming a likelihood of a set of structure factors $\{F_h\}$ for the experimental crystal structure as (1) the likelihood of having obtained an observed
5 set of structure factors $\{F_h^{OBS}\}$ if structure factor set $\{F_h\}$ was correct, and (2) the likelihood that an electron density map resulting from $\{F_h\}$ is consistent with selected prior knowledge about the experimental crystal structure; and

b. adjusting the set of structure factors $\{F_h\}$ to maximize the likelihood of $\{F_h\}$ for the experimental crystal structure.

7. A method according to Claim 6, wherein forming the likelihood of $\{F_h\}$ further includes forming the likelihood that $\{F_h\}$ is compatible with selected other prior knowledge of the experimental crystal structure.

8. A method according to Claim 6, wherein the step of adjusting the structure factors includes the steps of (1) determining the response of the likelihood of $\{F_h\}$ to changes in the electron density map and (2) determining the response of the electron density map to changes in $\{F_h\}$.

9. A method according to Claim 6, further including the step of approximating the likelihood of the electron density map includes the step of forming a Taylor's series expansion of the likelihood of the electron density map and evaluating the terms of the Taylor's series expansion through a Fast Fourier
5 Transform.

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